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Initial treatment of steroid-sensitive idiopathic nephrotic syndrome in children with mycophenolate mofetil vs. prednisone: A randomized, controlled, multicenter trial (INTENT Study)

For peer review

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024882
Article Type:	Protocol
Date Submitted by the Author:	21-Jun-2018
Complete List of Authors:	Ehren, Rasmus; Children's and Adolescent's Hospital, University Hospital of Cologne, Pediatric Nephrology Benz, Marcus; Children's and Adolescent's Hospital, University Hospital of Cologne, Pediatric Nephrology Doetsch, Jorg; Children's and Adolescent's Hospital, University Hospital of Cologne Fichtner, Alexander; University Children's Hospital, Heidelberg Gellermann, Jutta; University Hospital Berlin Charité Department of Pediatrics University Children's Hospital Berlin Haffner, Dieter; University Hospital Hannover Department of Pediatrics University Children's Hospital Hannover Höcker, Britta; University Children's Hospital, Heidelberg Hoyer, Peter; University Hospital Essen Department of Pediatrics University Children's Hospital Essen Kästner, Bärbel; KKS (Coordination Center for Clinical Trials) Heidelberg am Universitätsklinikum Heidelberg Kemper, Markus; Asklepios Klinik Nord – Heidberg, Department of Pediatrics Konrad, Martin; University Hospital Münster Department of Pediatrics University Children's Hospital Münster Luntz, Steffen; KKS (Coordination Center for Clinical Trials) Heidelberg am Universitätsklinikum Heidelberg Querfeld, Uwe; University Hospital Berlin Charité Department of Pediatrics University Children's Hospital Berlin Sander, Anja; University of Heidelberg Institute of Medical Biometry and Informatics Toenshoff, Burkhard; University Children's Hospital, Heidelberg Weber, Lutz; Children's and Adolescent's Hospital, University Hospital of Cologne, Pediatric Nephrology
Keywords:	Mycophenolat mofetil, steroid-sensitive nephrotic syndrome, steroids, alternative treatment

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Initial treatment of steroid-sensitive idiopathic nephrotic syndrome in children with mycophenolate mofetil *vs.* prednisone:

A randomized, controlled, multicenter trial (INTENT Study)

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Abstract

Introduction

Idiopathic nephrotic syndrome is the commonest glomerular disease in childhood with an incidence of 1.8 cases per 100.000 children in Germany. The treatment of the first episode implies two aspects: induction of remission and sustainment of remission. The recent KDIGO, American Academy of Pediatrics (AAP) and German guidelines for the initial treatment of the first episode of a nephrotic syndrome recommend a 12-week-course of prednisone. Even though being effective, this treatment is associated with pronounced glucocorticoid-associated toxicity due to high-dose prednisone administration over a prolonged period of time. The aim of the INTENT study is to show that an alternative treatment regimen with mycophenolic acid is not inferior regarding sustainment of remission but with lower toxicity compared to treatment with glucocorticoids only.

Methods and design

The study is designed as an open, randomized, controlled, multicenter trial. 340 children with a first episode of steroid-sensitive nephrotic syndrome and achieved remission by a standard prednisone regime will be enrolled in the trial and randomized to one of two treatment arms. The standard care group will be treated with prednisone for a total of 12 weeks; in the experimental group the treatment is switched to mycophenolate mofetil, also for a total of 12 weeks treatment duration. The primary endpoint is the occurrence of a treated relapse within 24 months after completion of initial treatment. This study is funded by the German Federal Ministry of Education and Research.

Ethics and dissemination

Ethics approval for this trial was granted by the ethics committee of the Medical Faculty of the University of Heidelberg (AFmu-554/2014). The study results will be published in accordance with the CONSORT statement and SPIRIT guidelines. Our findings will be submitted to major international pediatric nephrology and general pediatric conferences and submitted for publication in a peer-reviewed open access journal.

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Trial registration: European Clinical Trials Database EudraCT No.: 2014-001991-76

Date of registration: October 30, 2014

Deutsches Register Klinischer Studien – German clinical trials register

DRKS00006547

Date of registration: Februar 24, 2017

Keywords: Mycophenolat mofetil; steroid-sensitive nephrotic syndrome, steroids, alternative treatment

Article summary

Strengths and limitations of this study

- This is the first trial worldwide that prospectively evaluates a steroid-reduced initial treatment alternative for childhood nephrotic syndrome
- This trial has the potential to reduce steroid-associated side effects without losing efficacy
- If our hypotheses turn out to be true, the experimental therapy has the potential to become the future standard of care
- This is one of the few randomized, controlled, prospective, multicenter trials in pediatric nephrology, but due to clinical and financial aspects the trial is not blinded

Word count: 5688 words

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Introduction

Idiopathic nephrotic syndrome in childhood

Clinical course and epidemiology

Idiopathic nephrotic syndrome in childhood, defined as the combination of heavy proteinuria (>40 mg/m^2 body surface area (BSA) per h) and hypalbuminemia (<25 g/L), in general accompanied by edema and hyperlipidemia, is a rare, relapsing disease with an incidence of 1.8 per 100.000 children below 16 years of age in Germany (German registry of rare pediatric diseases, ESPED 2005-2006), resulting in an annual rate of 200-250 new patients.[1] The classification according to the four following categories is important for diagnostics, treatment and prognosis of nephrotic syndrome in childhood: etiology, age at onset, histology, response to glucocorticoids. The primary idiopathic nephrotic syndrome with a typical onset at 1-10 years of age should be differentiated from patients with secondary causes or patients with age at onset younger than one year (congenital and infantile forms) or older than 10 years of age. Approximately 80% of the children with idiopathic nephrotic syndrome have minimal change disease in renal biopsy and approximately 7% focal segmental glomerulosclerosis. The most important prognostic factor is steroid-sensitivity occurring in over 90% of the patients.

Treatment

The treatment of the first episode implies two aspects: induction of remission and sustainment of remission. The *Gesellschaft für Pädiatrische Nephrologie (GPN)*, formerly known as *Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN)*, defined the standard of care for children with nephrotic syndrome.[2–7] *The effectual guideline for the initial treatment of the first episode of a nephrotic syndrome recommends in detail: 60 mg*

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prednisone/m^2 BSA per day (maximum 80 mg/day) for 6 weeks followed by alternate day prednisone 40 mg/m^2 BSA (maximum 60 mg/48 hours) for another 6 weeks.[8]

In case of steroid-sensitivity remission usually occurs within 7-14 days of treatment; the overall duration of initial prednisone treatment is 12 weeks in order to sustain remission. This regimen is associated with a relapse rate of 51% within 24 months after initial prednisone therapy, and a rate of frequent relapses (definition: relapses occur 4 or more times in any 12 month period or 2 or more relapses within the first 6 months period after initial response) of 29% is expected.

Side effects of treatment

Even though being effective, this treatment is associated with pronounced glucocorticoid associated toxicity due to high-dose prednisone administration over a prolonged period of time.

The major side effects, which have been shown consistently in previous studies,[3, 4, 9] comprise obesity, striae, hypertrichosis, cataract, glaucoma, arterial hypertension, psychological disturbances, growth failure, disturbances in carbohydrate and lipid metabolism, osteopenia, and avascular bone necrosis. Not all of these side effects are completely reversible after cessation of steroid therapy. In one study for example, excessive gain of weight during initial steroid therapy persisted in a significant subset (47%) of patients following cessation of glucocorticoid therapy.[10] Obesity following cessation of glucocorticoid therapy was associated with hyperlipidemia, which might enhance the cardiovascular risk of these patients in the long run.[11] Other studies have shown that exposure to higher doses of glucocorticoids in the initial therapy leads to more toxicity without prevention of future relapses.[12–15]

Role of mycophenolate mofetil in the treatment of nephrotic syndrome in childhood

Mycophenolate mofetil (MMF), the pro-drug of its active moiety mycophenolic acid (MPA), is a

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potent, selective and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), the key enzyme of *de novo* purine synthesis in activated lymphocytes. MMF is effective in sustaining remission in patients with frequently relapsing or glucocorticoid-dependent nephrotic syndrome.

Four prospective studies in patients with frequently relapsing or glucocorticoid-dependent nephrotic syndrome receiving a long-term therapy with MMF explored the possibility of withdrawing prednisone, which was successful in >50% of patients without further relapses.[16–19] In children with glucocorticoid-dependent nephrotic syndrome on MMF, Dorresteijn et al. reported relapse rates of 25% after 6 months and 45% after 12 months, respectively.[20] In a phase II Bayesian trial, Baudouin et al. confirmed the effect of MMF in reducing relapse rates and in sparing glucocorticoids in children with glucocorticoid-dependent nephrotic syndrome.[21] A recent GPN study on the maintenance of remission in children with frequently relapsing or steroid-dependent nephrotic syndrome has shown that MMF in adequate exposure is as effective as cyclosporine A (CSA) in sustaining remission without the burden of CSA-induced nephrotoxicity.[22]

So far, no studies with MMF for the initial treatment of the steroid-sensitive nephrotic syndrome (SSNS) in children have been performed. However, it seems coherent to use the efficacy of MMF also for sustaining remission in the initial treatment of SSNS and to benefit from its lower toxicity compared to glucocorticoids.

Rationale

The initial treatment of the idiopathic nephrotic syndrome in children requires sufficient immunosuppressive therapy, but should avoid toxicity, since the intensity of the initial treatment does not influence the long-term course of the disease. For example, a GPN trial on the initial treatment of nephrotic syndrome revealed no overall advantage of an intensified

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immunosuppressive protocol adding CSA in terms of occurrence of relapses during a follow-up of 24 months.[5, 12, 13]

Our hypothesized novel treatment protocol has the potential to reduce the burden of glucocorticoid-associated side effects and associated cardiovascular risk factors, if the novel protocol is not inferior to the standard therapy regarding sustainment of remission. If our hypothesis turns out to be true, this novel therapy has the potential to become the standard of care for the initial treatment of SSNS in children.

Methods/design

Aim

The main purpose of the study is to show that MMF in the initial treatment of SSNS in children is not inferior regarding maintenance of initial remission and subsequent relapse rate compared to the standard prednisone regimen.

Study design

This is a prospective, randomized, multicenter, controlled, open, parallel group phase III non-inferiority trial.

After initiation of the study, patients will be screened consecutively and eligible patients will be enrolled into the study at each center.

Each sites' principal investigator has to declare to the coordinating investigator/sponsor that he/she will conduct the study according to the protocol, ethical rules, and to provide the support as needed. To minimize a potential performance bias, this will be fixed in a contract prior to commencing the study. The clinical monitor will introduce the sites in detail to study procedures and documentation in advance.

Bias by potential influential factors will be addressed by inclusion as covariates into the statistical analysis. Independent clinical on-site monitoring to ensure patients safety and

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integrity of the clinical data in adherence to study protocol will focus on source data documentation, correctness of data, and adherence to study procedures, e.g. randomization and treatment.

Based on the performed interventions and planned analysis blinding is not feasible to minimize bias, because the interventions can easily be differentiated due to visible side effects such as obesity, which is only expected in the standard care group. Furthermore, MMF is used in liquid form as a suspension and prednisone as a tablet. However, the primary endpoint is based on standardized diagnostic work-up results, i.e. objective criteria.

The duration of the study for each subject is expected to be 27 months (including 24 months follow-up after intervention). (Figure 1 and Figure 2)

Patient and public involvement

Patients were not directly involved in the study development and design. Repeated discussions with patient representatives beforehand showed one of their main wishes that is reduction of steroids in the treatment of nephrotic syndrome.

We generated an information document for parents in form of a flyer that was distributed also to patient initiatives. Spreading out information on the study shall improve recruitment. There is no patient adviser involved in the conduct of the study, neither was the burden of the intervention assessed by patients or their parents during study development.

Study results will be published open access. Patients and their representatives will be informed through meetings and a brief summary of the results distributed by local investigators.

Recruitment

The study is conducted on a multicenter basis. The rarity of the disease requires a nationwide recruitment. The planned 35 study centers are evenly distributed over

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Germany. Each study center is coordinating a number of collaborating hospitals and practitioners that will transfer eligible patients with primary onset steroid-sensitive nephrotic syndrome for screening, enrollment, randomization and study visits. 400 patients should be assessed for eligibility, 340 subjects should be enrolled in the clinical study, i.e. 170 subjects per treatment group.

Inclusion criteria and exclusion criteria

Inclusion criteria

Subjects meeting all of the following criteria will be considered for admission to the study:

- First episode of SSNS
- *Remission induced by prednisone or prednisolone 60 mg/m^2 BSA (maximum 80 mg/day) per day within 28 days*
- Male and female children aged ≥ 1 year and ≤ 10 years at beginning of the study (typical age range of patients with SSNS)
- Ability of the persons having care and custody of the child to understand character and individual consequences of clinical study
- Written informed consent of the persons having care and custody of the child (must be available before enrollment in the study)

Exclusion criteria

Subjects presenting with any of the following criteria will not be included in the study:

- Secondary nephrotic syndrome
- Estimated glomerular filtration rate (eGFR) <90 mL/min x 1.73 m^2 BSA
- Ongoing treatment with systematically administered glucocorticoids or other immunosuppressive drugs at time of first episode of nephrotic syndrome
- Hemoglobin concentration of ≤90 g/L (SI unit)
- Leucocyte count of ≤2.5 x 10^9/L (SI unit)

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- Severe chronic gastrointestinal disease
- History of hypersensitivity to MMF or to any drug with similar chemical structure or to any excipient present in the pharmaceutical form of suspension of MMF (CellCept® suspension)
- Refusal of subject
- Participation in other clinical studies or observation period of competing studies

Study medication

The sponsor, i.e. the University Hospital Heidelberg, will provide the required study medication (mycophenolate mofetil, CellCept® suspension). Careful records will be kept of the study medication supplied to the centers and distributed to the patients.

Prednisone is used as standard therapy following the definition of the *GPN* (standard treatment) and is prescribed as usual.

- Prednisone or prednisolone (control intervention)

- MMF is administered in liquid form (CellCept® suspension (Roche Registration Ltd.)) (experimental intervention)

Adherence

Adherence will be recorded by the patients' diary.

Screening

All patients who seem suitable for study participation and take part in the screening will receive a screening number and will be registered in a screening log. Together with the center ID this will be the unique identification number throughout the study.

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Parents of children with initial episode of idiopathic nephrotic syndrome aged between 1 and 10 years and treated with standard regime (prednisone 60 mg/m^2 BSA per day) will be informed about the ongoing INTENT study. If the child fulfills the inclusion criteria the persons having care and custody of the child and the patient, if ≥6 years of age, will be formally elucidated about the INTENT study by the study center in a form understandable to him or her and asked for written assent/consent.

For checking the exclusion criteria concerning eGFR, leucocyte count and hemoglobin concentration the most recent lab values should be used; they should have been obtained no more than 28 days prior to visit 1.

Randomization

To achieve comparable intervention groups, patients will be allocated in a concealed fashion by means of randomization using a centralized web-based tool (www.randomizer.at). Randomization will be performed stratified by age groups (grouped: <7 years of age, ≥7 years of age), because age is known to influence the occurrence of relapses. If the randomizer is not available in urgent cases the Institute of Medical Biometry and Informatics can be contacted and a biometrician or data manager will perform the randomization.

Intervention

Maximum duration of treatment is 12 weeks after first day of initial treatment of SSNS. (Figure 1)

Control intervention

• Prednisone, which is continued for a total of 6 weeks with the dosage of 60 mg/m^2 BSA/d (maximum 80 mg), is given twice per day or three times per day

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plus

- Prednisone, which is given for another total of 6 weeks with the dosage of 40 mg/m^2 BSA (maximum 60 mg) on alternate days (every other day) in one dose in the morning

Resorption of prednisone is independent of food intake.

Experimental intervention

- MMF is given in a dosage of 1200 mg/m^2 BSA/d as a suspension (200 mg/mL) until 12 weeks total treatment duration. MMF is given twice a day, i.e. every 12 hours (± one hour)
- The suspension of MMF is prepared in the study center (according to the summary of product information)
- The persons having care and custody of the child are informed that MMF should be given 30 minutes before or 60 minutes after food intake.
- For the first two weeks from randomization on, prednisone is given with the dosage of 40 mg/m^2 BSA (maximum 60 mg) on alternate days (every other day) in one dose in the morning.
- *At Visits 2 and 3 MPA-exposure is measured by a limited sampling strategy (blood samples are obtained at time points 0, 1 and 2 hours after intake of MMF*

Recording of primary endpoint

Daily dipstick testing of urine (Albustix®) and documentation in a standardized diary by a person having care and custody of the child is common current practice in the care of patients with nephrotic syndrome in pediatric nephrology centers.

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No guideline exists on whether standard relapse treatment with prednisone should be started immediately when definition of relapse is fulfilled to avoid the associated complications of an edematous relapse or whether treatment should be delayed for several days to determine whether proteinuria resolves spontaneously. Therefore, in the INTENT study a time period of up to 10 days is allowed for a possible spontaneous remission, before standard therapy for relapse is started.

Treatment of a relapse has to be performed according to standard therapy of the *GPN*. Relapses with and without treatment are documented in the eCRF.

Treatment of frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome with other medications than prednisone is carried out according to center practice, because there is no internationally accepted guideline on this topic. The performed treatment with immunosuppressive agents such as CSA, tacrolimus, MMF, cyclophosphamide, rituximab, or levamisole is documented in the eCRF.

After completion of the study, patients will be treated according to center practice.

Outcome measures

Primary study endpoint

The primary efficacy endpoint is occurrence of a treated relapse within 24 months after completion of initial treatment. The rationale is that this endpoint was chosen in all previous studies on the initial treatment of SSNS in children and is also the primary endpoint in various meta-analyses on this topic.[3–5, 7, 8]

Definition of relapse: Relapse is denoted by a reappearance of proteinuria for 3 consecutive days:

Albustix® ≥2+ (first or second morning urine)

or

urine protein/creatinine (Up/c) ratio ≥2 g/g (first or second morning urine)

or

urine protein excretion of ≥40mg/m^2 BSA/h (urine collection for minimum 12 hours)

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Relapses with and without treatment are documented. The primary endpoint is fulfilled by the first treated relapse.

Secondary endpoints

Secondary endpoints are divided into five items:

1. Course of the disease as described by the following criteria
    a. Time from remission to first relapse
    b. Number of relapses during follow-up
    c. Mean relapse rate per patient and year
    d. Number of frequent relapsers
    e. Time from remission to intensification of immunosuppressive treatment with other drugs due to glucocorticoid-induced toxicity
    f. Rate of patients who require more intense immunosuppressive treatment
2. Glucocorticoid-associated toxicity:
    a. Cumulative prednisone dose as mg/m^2
    b. As there is no validated score for glucocorticoid-induced toxicity, each item is registered separately. At study visits 1-8, body mass index, blood pressure, and growth will be checked for quantitative influence, striae, hypertrichosis, acne, and psychological disturbances by yes or no for qualitative influence. Additionally, at study visits 1, 5, and 8, patients will be checked for cataract and glaucoma (by yes or no).
3. MMF-associated toxicity: At all visits, patients will be checked for known side effects of MMF, especially diarrhea, blood cell count disturbance, and infections.
4. Health-related quality of life, which may be impaired in children with nephrotic syndrome will be measured with a validated questionnaire (DISABKIDS) at visits 1/5/8.

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5. Days missing school attendance and days of hospitalization will be documented as a measure for the impact of the disease on everyday life.

It is expected that the MMF-based regimen will avoid acute and long-term glucocorticoid-associated toxicity and is therefore superior regarding the benefit/risk ratio. However, this will not be tested confirmatorily, since there is no endpoint or score summarizing the different aspects of side effects.

Statistical considerations

Sample size calculation

The sample size calculation is based on the primary efficacy endpoint "occurrence of a treated relapse within 24 months after completion of the initial treatment". In the literature varying information is given regarding the relapse rate for the control group receiving standard prednisone therapy. We have decided to assume a relapse rate of 51% according to Gipson et al.[8] The same rate is expected for the experimental group. If the relapse rate in the experimental group accounts to less than 15% above the relapse rate of the control group, this will be considered as clinically irrelevant based upon clinical judgement. Therefore the margin is set to δ=0.15. As the direction of the difference to be established is known for non-inferiority studies and as - due to the rareness of the disease and the related limited available number of patients - the study could otherwise not be performed with sufficient power, a one-sided significance level of 5% is applied. Testing at a one-sided significance level of α = 5% and aspiring a power of 80%, a total of 272 patients (136 per group) are required (calculations performed with ADDPLAN 6.0). To account for a 10% drop-out rate and major protocol violations in a further 10%, 340 patients will be randomized.

Adherence/Rate of loss of follow up

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The nephrotic syndrome in children is mostly an acutely presenting disease, and parents are very concerned about their child. With standard prednisone treatment we observe a high adherence to therapy. According to our previous experience in performing studies in pediatric nephrology we assume that a minimum of 85% of patients assessed for eligibility will be allocated to the study [4, 5, 22]. Due to the exclusive care of these patients in specialized pediatric nephrology centers we calculate with a loss of follow-up either due to drop-out or major protocol violation of maximum 20% which corresponds to our previous studies.[4, 5, 22] The recent study of the GPN, showing that MMF is efficacious in sustaining remission in children with frequently relapsing nephrotic syndrome, had only a drop-out rate of 4%. Therefore, for the entire study, we estimated 400 children with steroid-sensitive nephrotic syndrome to be assessed for eligibility, 340 to be allocated to study and 272 patients to be analyzed per protocol. However, in cases of premature withdrawal by a patient the persons having care and custody of this patient will be asked for informed consent so that routinely recorded data by the covering physician can be used for the INTENT study. In this manner as many data as possible is recorded for evaluation of treatments in this rare disease.

Analysis populations

The primary analysis will be performed for both the per-protocol population (PP) and the intention-to-treat population (ITT). The PP population comprises all patients, who were treated according to the randomized treatment as outlined in the protocol without major protocol violations (e.g., reduction of study medication of >50% or interruption of study medication of >3 days, violation of in- or exclusion criteria).The ITT population will comprise all patients randomized into the study. In this set, every patient is analyzed according to the group randomized into.

Since there may be patients who withdraw from the study after the treatment period or within the treatment period but consent to the analysis of routinely recorded data was given the inclusion of these patients into the ITT population will be decided case by case before database lock and defined when writing the statistical analysis plan (SAP). As appropriate, a third population will be defined for

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analysis of the primary and important secondary endpoints. How to deal with these patients and their data in detail depends on the time point of withdrawal and the amount and reliability of the routinely collected data.

The safety set will comprise all patients who have received study medication at least once, and will allocate the patients to the treatment they actually received, regardless of randomization. Whether routinely collected data of patients who withdraw prematurely can be included herein depends on the reliability of the collected safety data.

Statistical methods

The non-inferiority of the experimental group *vs.* control group will be evaluated using the test according to Farrington and Manning. The one-sided significance level is set to 5%.

The hypotheses to be assessed in the primary efficacy analysis are formulated as follows:

H_0: p_MMF – p_Prednisone ≥ δ (δ=0.15, non-inferiority margin, see sample size calculation for justification)

H_1: p_MMF – p_Prednisone < δ, where p_* denotes the relapse rate in the respective group.

Before database closure the assignment of patients to the PP population (patients with no major protocol violations) and the ITT population (as classified by the intent-to-treat principle) are defined in the statistical analysis plan. The confirmatory analysis is performed for both the PP population and the ITT population. This approach reflects the equal importance of both analysis sets in a non-inferiority trial. For the PP analysis missing values for the primary endpoint are not expected. In the ITT population missing values will be replaced according to Higgins.[23] As appropriate, a third population will be defined to adequately incorporate routinely collected data of patients who withdraw prematurely but gave informed consent for usage of routinely collected data. Details on inclusion of such data into sensitivity analyses of primary and secondary endpoints will be defined in

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more detail in the SAP. In case of uncertainty regarding data quality and reliability these patients will only be analyzed descriptively.

Additionally, binary logistic regression models will be performed as sensitivity analysis for the intervention comparison of the relapse rates adjusting for age, gender, center (grouped), and for results of therapeutic drug monitoring (grouped) based on different populations (PP, ITT, with values of drop-outs set to worst case).

All secondary outcomes will be evaluated descriptively, using appropriate statistical methods based on the underlying distribution of the data. Descriptive p-values are reported together with 95% confidence intervals for the corresponding effects. Descriptive statistics for continuous parameters and scores include number of non-missing observations, mean, standard deviation, median, minimum and maximum, performed for treatment groups as well as subgroups and overall. The description of categorical variables (ordinal or nominal) includes the number and percentage of patients belonging to the relevant categories in the study population as well as to each treatment group.

Rates of adverse and serious adverse events will be calculated with 95% confidence intervals for treatment group comparisons.

Statistical methods are used to assess the quality of the data, homogeneity of treatment groups, endpoints and safety of the two intervention groups. Details of the statistical analysis will be fixed at the latest in the SAP to be prepared within the first year after start of patient recruitment. All persons taking part in the preparation of the SAP and possible later changes to it will only have access to blinded data to avoid introduction of bias.

Interim Analyses

No interim analysis will be performed for the following reason: The recruitment phase is planned to be 36 months. The primary endpoint is occurrence of treated relapse within 24 months after end of initial treatment. Therefore, information on the primary endpoint for a first portion of the study

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patients will be available not before end of the recruitment phase. For this reason, a group-sequential approach was not pursued.

However, an independent data safety monitoring board (DSMB) will closely monitor the recruitment, the reported adverse events, the data quality of the study and the occurrence of potential early relapses during the intake of MMF, thus ensuring the ethical conduct of the study and protecting the safety interests of patients.

Adverse events

Adverse events (AEs) will be ascertained by the investigators using non-leading questions, noted as spontaneously reported by the patients to the medical staff or observed during any measurements on all study days. The observation period begins with the first administration of the Investigational Medicinal Product and ends with visit 4, (i.e. 6 months after day 1 [= first day of treatment with standard therapy]). The patient or his primary care physician should report any AE during the outpatient period via phone to the investigator.

AEs will be documented in the patient file and in the electronic case report form (eCRF). All subjects who present AEs,

whether considered associated with the use of the study medication or not, will be monitored by the responsible investigator to determine their outcome; this applies to withdrawals, too.

All serious adverse events (SAEs) and their relevance for the benefit/risk assessment of the study will be evaluated continuously during the study and for the final report.

All SAEs must be reported by the investigator to the Department of Pharmacovigilance at the Coordination Center for Clinical Trials (KKS) Heidelberg within 24 hours after the SAE becomes known using the "Serious Adverse Event" form.

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Suspected unexpected serious adverse events (SUSARs) are to be reported to the responsible ethics committee, the competent authority and to all participating investigators within defined timelines, i.e. they are subject to an expedited reporting.

All SAEs will be subject to a second assessment by a designated person or his deputy, who will be independent from the reporting investigator.

Data management

Data management and quality assurance

The investigator or a designated representative must enter all protocol-required information in the eCRF. The eCRF should be completed as soon as possible after the information is collected, preferably on the same day when a study subject is seen for an examination, treatment, or any other study procedure. The reason for missing data should be provided. The investigator is responsible for ensuring that all sections of the eCRF are completed correctly and that entries can be verified in accordance with the source data. Any entry and correction in the Remote Data Entry System will be documented automatically in an audit file.

Completeness, validity and plausibility of data will be checked in time of data entry (edit-checks) and using validating programs, which will generate queries. The investigator or the designated representatives are obliged to clarify or explain the queries. If no further corrections are to be made in the database it will be closed and used for statistical analysis. All data management procedures will be carried out on validated systems and according to the current Standard Operating Procedures (SOPs) of the Institute of Medical Biometry and Informatics (IMBI) of the University of Heidelberg.

Ethical and Legal Aspects

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that all persons involved in the study abide by International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human

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Use harmonized tripartite guideline on Good Clinical Practice (ICH-GCP) and the ethical principles described in the applicable version of the Declaration of Helsinki.

The study will be carried out in conformity with the ICH Topic E6, Guideline for Good Clinical Practice, including post Step 4 errata, September 1997, Directive 2001/20/EC (April 4, 2001), Commission Directive 2005/28/EC (April 8, 2005), National regulatory requirements/guidelines of the participating countries concerning Clinical Studies [e.g. federal drug law (AMG), GCP ordinance (GCP-Verordnung), Medical device law (MPG)], general national regulatory requirements, e.g. Bundesdatenschutzgesetz (BDSG).

Ethics committee approval

Ethical approval of the INTENT study was granted by the ethics committee of the Medical Faculty of the University of Heidelberg (AFmu-554/2014) on March 18, 2015. This approval has subsequently been confirmed by the local ethics committees of all participating centers. A list of all local ethics committees and all participating centers is provided as an additional file.

The latest version of the trial protocol (version 5.0) was approved by the ethics committee on June 01, 2016.

Approval of the regulatory authorities

According to the German Federal law the study was approved by the Federal Institute of Drugs and Medical Devices on April 02, 2015 (reference number 61-3910-4040246). The latest version of the trial protocol (version 5.0) was approved by the Federal Institute of Drugs and Medical Devices on July 11, 2016.

Discussion

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Risk-benefit Assessment

Neither intensification nor prolonging initial therapy has influenced long-term prognosis of SSNS in terms of number of relapses and risk of frequent relapses [12–15]. MMF is effective in sustaining remission in patients with frequently relapsing steroid-sensitive nephrotic syndrome [16, 21, 22]. Therefore we hypothesize that after initial remission is achieved the risk for immediate relapse will not be increased in the experimental group. If a patient of the experimental group develops a relapse under MMF therapy he or she will be given prednisone anyway for induction of remission; the overall prognosis would therefore not be influenced. On the other hand, the patients in the experimental group may have the potential to benefit significantly because of less glucocorticoid-associated toxicity.

The most frequently observed side effects of MMF are gastrointestinal symptoms such as nausea, vomiting, stomach pain and diarrhea and hematological symptoms such as leukopenia, anemia and rarely thrombocytopenia and an enhanced susceptibility for infections. In general, these side effects occur more frequently and have a higher clinical significance, when MMF is administered in conjunction with other immunosuppressive medication such as CSA or tacrolimus, as indicated after solid organ transplantation. When MMF is administered as monotherapy, for example in patients with frequently relapsing steroid-sensitive nephrotic syndrome, the frequency and severity of these side effects are markedly lower [16–21]. Side effects will be systematically evaluated during the trial visits.

In order to acknowledge recently reported adverse events (hypogammaglobinemia, bronchiectasis, the risk of terato- and mutagenity) in patients after solid organ transplantation and treated with MMF in conjunction with other immunosuppressive medications in the long-time run, these adverse events are also monitored closely in the INTENT study, despite these events are very unlikely to occur due to the short administration period of MMF (max. 11 weeks) and the age group being tested in this trial.

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The oral formulation of MMF being a suspension allows exact and flexible dosing and reliable administration even to small children.

Cost-benefit analysis

The costs for a treatment with mycophenolic acid for an average time of 74 days (84 days of initial treatment minus an average of 10 days till remission) in a child with a body surface area of 0.8 m² in Germany are approximately ten times higher than the standard treatment with prednisone (500 € compared to 50 €). With the expected 250 new cases of childhood nephrotic syndrome per year this would mean extra costs of about 110.000 € for the German health care system. On the other hand, it has been shown that excessive weight gain during the initial steroid therapy in a significant subset (47%) of patients after cessation of glucocorticoid therapy persisted and thus contributes to long-term cardiovascular risk.[10, 11] These potential extra costs are hardly to be calculated but it seems reasonable enough to avoid long-term effects of high dose prednisone treatment.

Potential impact

The current study continues the long-lasting tradition of prospective randomized trials on the initial treatment of idiopathic nephrotic syndrome performed by the *GPN* (formerly *Arbeitsgemeinschaft für Pädiatrische Nephrologie*).

This is the first trial worldwide that prospectively evaluates a steroid-reduced initial treatment alternative that has the potential to reduce the number of side effects without lacking efficacy. If our hypotheses turn out to be true, the experimental therapy has the potential to become the future standard of care.

Optimizing recruitment

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Our structure of numerous study centers covering entire Germany that collaborate with regional hospitals and practitioners should make most new manifestations of idiopathic nephrotic syndrome available to study evaluation.

Nevertheless patient recruitment currently stays behind schedule. One aspect to improve recruitment is initiation of further study centers especially in densely populated areas in Southern Germany. Other aspects are strengthening the motivation of collaborating partners to transfer patients, advertising the study in widely distributed journals, by personal contact via mail and phone and to introduce the study at all suitable annual conferences. If patient recruitment cannot be increased sufficiently by these measures the recruitment period has to be prolonged.

Dissemination

The study results will be published in accordance with the CONSORT statement and SPIRIT guidelines. Our findings will be submitted to major international pediatric nephrology and general pediatric conferences and submitted for publication in a high impact factor journal with open access.

Trial status

The recruitment of the study started in October 2015.

As of June 12, 2018 a total of 156 children have been recruited into the study.

List of abbreviations

AAP	American Academy of Pediatrics
AE	Adverse event
AMG	Arzneimittelgesetz (German Medicinal Products Act)
APN	Arbeitsgemeinschaft für Pädiatrische Nephrologie

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BMBF	Bundesministerium für Bildung und Forschung (German Federal Ministry of Education and Research)
BSA	Body surface area
CSA	Cyclosporine A
DSMB	Data safety monitoring board
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ESPED	Erhebungseinheit für Seltene Pädiatrische Erkrankungen in Deutschland (German registry of rare pediatric diseases)
GCP	Good Clinical Practice
GPN	Gesellschaft für Pädiatrische Nephrologie (Society of Pediatric Nephrology)
ICH-GCP	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use harmonized tripartite guideline on Good Clinical Practice
IMBI	Institute of Medical Biometry and Informatics
IMPDH	Inosine monophosphate dehydrogenase
ITT	Intention-to-treat
KDIGO	Kidney Disease| Improving Global Outcomes
MMF	Mycophenolate mofetil
MPA	Mycophenolic acid
MPG	Medizinproduktegesetz (Act on Medical Devices)
PP	Per-protocol
SAE	Severe adverse event
SAP	Statistical analysis plan
SOP	Standard Operating Procedure
SSNS	Steroid-sensitive nephrotic syndrome

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SUSAR	Suspected unexpected severe adverse event

Declarations

Ethics approval and consent to participate

Ethics approval of the INTENT study was granted by the ethics committee of the Medical Faculty of the University of Heidelberg (AFmu-554/2014) on March 18, 2015. Informed consent will be/has been obtained from all participants.

Consent for publication

Not applicable.

Availability of data and material

http://www.intent-study.de

Competing interests

RE, MRB, JD, AF, JG, DH, BH, PFH, BK, MJK, MK, SL, UQ and AS declare to have no competing interests. BT and LTW have received research grants from Roche Pharma AG and Novartis AG.

Funding

The INTENT study is funded by the German Federal Ministry of Education and Research (BMBF, funding reference number 01KG1301).

Authors contributions

MRB, LTW, BT, JD, JG, DH, PFH, MJK, MK, UQ, AF, AS, RE designed the study. AS, MRB, RE, BT and LTW will undertake data analyses. BK and SL gave advice in regulatory affairs and in realization of the

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study. RE, MRB, BT and LTW wrote the first draft of this manuscript, which has been critically revised by all co-authors. All authors have read and approved the final version of the manuscript.

Acknowledgements

Not applicable.

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Legends to figure 1 and 2:

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Figure 1: Trial schema. On alternate days = every second day, BSA = body surface area

Figure 2: Study visit schedule. TDM MPA = therapeutic drug monitoring of mycophenolic acid, ABPM = ambulatory blood pressure monitoring, HRQoL = health related quality of life, *only in the experimental group

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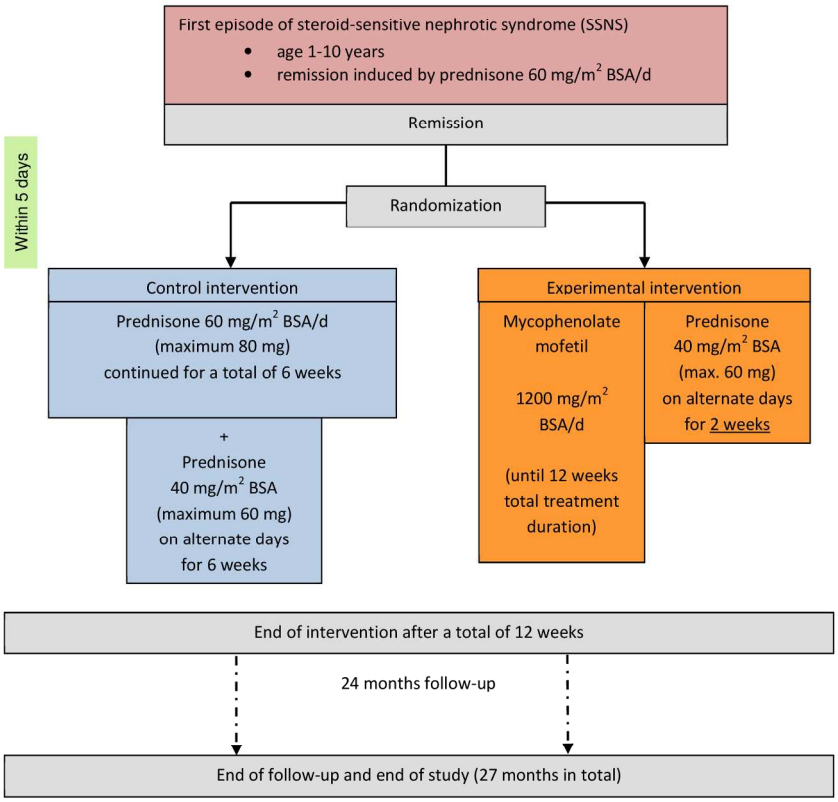

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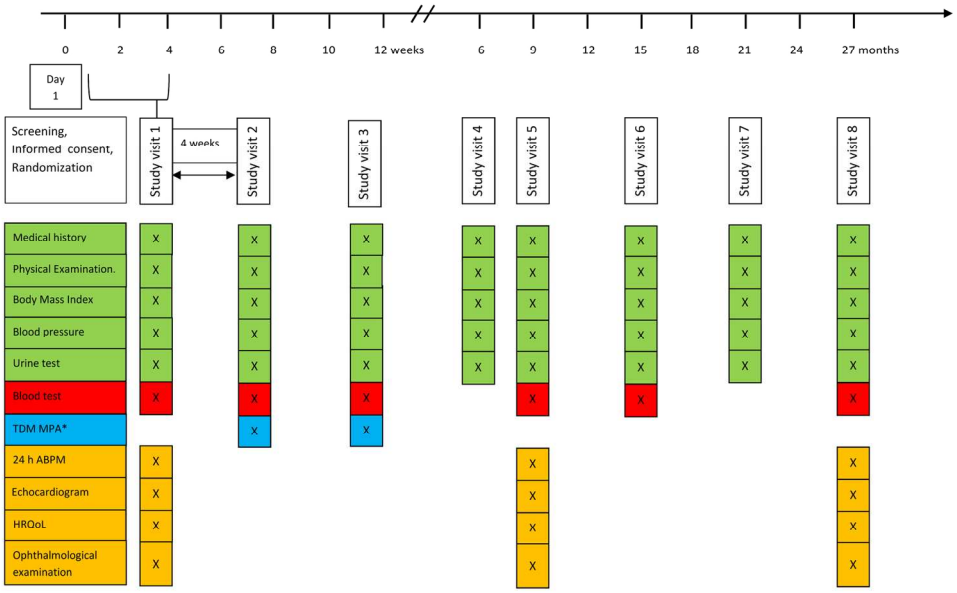

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____5_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____-_____
Protocol version	3	Date and version identifier	_____
Funding	4	Sources and types of financial, material, and other support	_____4_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____1-3_____
	5b	Name and contact information for the trial sponsor	see study protocol
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____

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Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____6,7_____
	6b	Explanation for choice of comparators	_____9_____
Objectives	7	Specific objectives or hypotheses	_____8_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____9_____

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	___10_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_____10,11__
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____13_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_see study protocol___
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____12_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____14-16__
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	__Figure 2__

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____16_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10, 25
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____12_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____12____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____12_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	not applicable
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_see study protocol_____

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____21_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__17-19_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17-19
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	__see study protocol_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_20_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	20-21_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_see study protocol_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__27_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_see study protocol_____

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____12_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___27_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____-_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	See study protocol___
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____-_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__-_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_27_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	yes_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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BMJ Open

Initial treatment of steroid-sensitive idiopathic nephrotic syndrome in children with mycophenolate mofetil vs. prednisone: Protocol for a randomized, controlled, multicenter trial (INTENT Study)

For

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024882.R1
Article Type:	Protocol
Date Submitted by the Author:	30-Aug-2018
Complete List of Authors:	Ehren, Rasmus; Children's and Adolescent's Hospital, University Hospital of Cologne, Pediatric Nephrology Benz, Marcus; Children's and Adolescent's Hospital, University Hospital of Cologne, Pediatric Nephrology Doetsch, Jorg; Children's and Adolescent's Hospital, University Hospital of Cologne Fichtner, Alexander; University Hospital Heidelberg, Center for Child and Adolescent Medicine Gellermann, Jutta; University Hospital Berlin Charité Department of Pediatrics University Children's Hospital Berlin Haffner, Dieter; University Hospital Hannover Department of Pediatrics University Children's Hospital Hannover Höcker, Britta; University Hospital Heidelberg, Center for Child and Adolescent Medicine Hoyer, Peter; University Hospital Essen Department of Pediatrics University Children's Hospital Essen Kästner, Bärbel; KKS (Coordination Center for Clinical Trials) Heidelberg am Universitätsklinikum Heidelberg Kemper, Markus; Asklepios Klinik Nord – Heidberg, Department of Pediatrics Konrad, Martin; University Hospital Münster Department of Pediatrics University Children's Hospital Münster Luntz, Steffen; KKS (Coordination Center for Clinical Trials) Heidelberg am Universitätsklinikum Heidelberg Querfeld, Uwe; University Hospital Berlin Charité Department of Pediatrics University Children's Hospital Berlin Sander, Anja; University of Heidelberg Institute of Medical Biometry and Informatics Toenshoff, Burkhard; University Hospital Heidelberg, Center for Child and Adolescent Medicine Weber, Lutz; Children's and Adolescent's Hospital, University Hospital of Cologne, Pediatric Nephrology
Primary Subject Heading:	Paediatrics

Secondary Subject Heading:	Renal medicine, Pharmacology and therapeutics
Keywords:	steroid-sensitive nephrotic syndrome, steroids, alternative treatment, mycophenolate mofetil

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Initial treatment of steroid-sensitive idiopathic nephrotic syndrome in children with mycophenolate mofetil *vs.* prednisone: Protocol for a randomized, controlled, multicenter trial (INTENT Study)

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Abstract

Introduction

Idiopathic nephrotic syndrome is the commonest glomerular disease in childhood with an incidence of 1.8 cases per 100.000 children in Germany. The treatment of the first episode implies two aspects: induction of remission and sustainment of remission. The recent KDIGO, American Academy of Pediatrics (AAP) and German guidelines for the initial treatment of the first episode of a nephrotic syndrome recommend a 12-week-course of prednisone. Even though being effective, this treatment is associated with pronounced glucocorticoid-associated toxicity due to high-dose prednisone administration over a prolonged period of time. The aim of the INTENT study is to show that an alternative treatment regimen with mycophenolic acid is not inferior regarding sustainment of remission but with lower toxicity compared to treatment with glucocorticoids only.

Methods and design

The study is designed as an open, randomized, controlled, multicenter trial. 340 children with a first episode of steroid-sensitive nephrotic syndrome and achieved remission by a standard prednisone regime will be enrolled in the trial and randomized to one of two treatment arms. The standard care group will be treated with prednisone for a total of 12 weeks; in the experimental group the treatment is switched to mycophenolate mofetil, also for a total of 12 weeks treatment duration. The primary endpoint is the occurrence of a treated relapse within 24 months after completion of initial treatment. This study is funded by the German Federal Ministry of Education and Research.

Ethics and dissemination

Ethics approval for this trial was granted by the ethics committee of the Medical Faculty of the University of Heidelberg (AFmu-554/2014). The study results will be published in accordance with the CONSORT statement and SPIRIT guidelines. Our findings will be submitted to major international pediatric nephrology and general pediatric conferences and submitted for publication in a peer-reviewed open access journal.

Trial registration: European Clinical Trials Database EudraCT No.: 2014-001991-76

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Date of registration: October 30, 2014

Deutsches Register Klinischer Studien – German clinical trials register

DRKS00006547

Date of registration: Februar 24, 2017

Keywords: mycophenolate mofetil; steroid-sensitive nephrotic syndrome, steroids, alternative treatment

Article summary

Strengths and limitations of this study

- This is the first trial worldwide that prospectively evaluates a steroid-reduced initial treatment alternative for childhood nephrotic syndrome
- This trial has the potential to reduce steroid-associated side effects without losing efficacy
- If our hypotheses turn out to be true, the experimental therapy has the potential to become the future standard of care
- This is one of the few randomized, controlled, prospective, multicenter trials in pediatric nephrology, but due to clinical and financial aspects the trial is not blinded

Word count: 5688 words

Introduction

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Idiopathic nephrotic syndrome in childhood

Clinical course and epidemiology

Idiopathic nephrotic syndrome in childhood, defined as the combination of heavy proteinuria (>40 mg/m^2 body surface area (BSA) per h) and hypalbuminemia (<25 g/L), in general accompanied by edema and hyperlipidemia, is a rare, relapsing disease with an incidence of 1.8 per 100.000 children below 16 years of age in Germany (German registry of rare pediatric diseases, ESPED 2005-2006), resulting in an annual rate of 200-250 new patients.[1] The classification according to the four following categories is important for diagnostics, treatment and prognosis of nephrotic syndrome in childhood: etiology, age at onset, histology, response to glucocorticoids. The primary idiopathic nephrotic syndrome with a typical onset at 1-10 years of age should be differentiated from patients with secondary causes or patients with age at onset younger than one year (congenital and infantile forms) or older than 10 years of age. Approximately 80% of the children with idiopathic nephrotic syndrome have minimal change disease in renal biopsy and approximately 7% focal segmental glomerulosclerosis. The most important prognostic factor is steroid-sensitivity occurring in over 90% of the patients.

Treatment

The treatment of the first episode implies two aspects: induction of remission and sustainment of remission. The *Gesellschaft für Pädiatrische Nephrologie (GPN)*, formerly known as *Arbeitsgemeinschaft für Pädiatrische Nephrologie (APN)*, defined the standard of care for children with nephrotic syndrome.[2–7] *The effectual guideline for the initial treatment of the first episode of a nephrotic syndrome recommends in detail: 60 mg prednisone/m^2 BSA per day (maximum 80 mg/day) for 6 weeks followed by alternate day prednisone 40 mg/m^2 BSA (maximum 60 mg/48 hours)* for another 6 weeks.[8]

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In case of steroid-sensitivity remission usually occurs within 7-14 days of treatment; the overall duration of initial prednisone treatment is 12 weeks in order to sustain remission. This regimen is associated with a relapse rate of 51% within 24 months after initial prednisone therapy, and a rate of frequent relapses (definition: relapses occur 4 or more times in any 12 month period or 2 or more relapses within the first 6 months period after initial response) of 29% is expected.

Side effects of treatment

Even though being effective, this treatment is associated with pronounced glucocorticoid associated toxicity due to high-dose prednisone administration over a prolonged period of time.
The major side effects, which have been shown consistently in previous studies,[3, 4, 9] comprise obesity, striae, hypertrichosis, cataract, glaucoma, arterial hypertension, psychological disturbances, growth failure, disturbances in carbohydrate and lipid metabolism, osteopenia, and avascular bone necrosis. Not all of these side effects are completely reversible after cessation of steroid therapy. In one study for example, excessive gain of weight during initial steroid therapy persisted in a significant subset (47%) of patients following cessation of glucocorticoid therapy.[10] Obesity following cessation of glucocorticoid therapy was associated with hyperlipidemia, which might enhance the cardiovascular risk of these patients in the long run.[11] Other studies have shown that exposure to higher doses of glucocorticoids in the initial therapy leads to more toxicity without prevention of future relapses.[12–15]

Role of mycophenolate mofetil in the treatment of nephrotic syndrome in childhood

Mycophenolate mofetil (MMF), the pro-drug of its active moiety mycophenolic acid (MPA), is a potent, selective and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), the key enzyme of *de novo* purine synthesis in activated lymphocytes. MMF is

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effective in sustaining remission in patients with frequently relapsing or glucocorticoid-dependent nephrotic syndrome.

Four prospective studies in patients with frequently relapsing or glucocorticoid-dependent nephrotic syndrome receiving a long-term therapy with MMF explored the possibility of withdrawing prednisone, which was successful in >50% of patients without further relapses.[16–19] In children with glucocorticoid-dependent nephrotic syndrome on MMF, Dorresteijn et al. reported relapse rates of 25% after 6 months and 45% after 12 months, respectively.[20] In a phase II Bayesian trial, Baudouin et al. confirmed the effect of MMF in reducing relapse rates and in sparing glucocorticoids in children with glucocorticoid-dependent nephrotic syndrome.[21] A recent GPN study on the maintenance of remission in children with frequently relapsing or steroid-dependent nephrotic syndrome has shown that MMF in adequate exposure is as effective as cyclosporine A (CSA) in sustaining remission without the burden of CSA-induced nephrotoxicity.[22]

So far, no studies with MMF for the initial treatment of the steroid-sensitive nephrotic syndrome (SSNS) in children have been performed. However, it seems coherent to use the efficacy of MMF also for sustaining remission in the initial treatment of SSNS and to benefit from its lower toxicity compared to glucocorticoids.

Rationale

The initial treatment of the idiopathic nephrotic syndrome in children requires sufficient immunosuppressive therapy, but should avoid toxicity, since the intensity of the initial treatment does not influence the long-term course of the disease. For example, a GPN trial on the initial treatment of nephrotic syndrome revealed no overall advantage of an intensified immunosuppressive protocol adding CSA in terms of occurrence of relapses during a follow-up of 24 months.[5, 12, 13]

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Our hypothesized novel treatment protocol has the potential to reduce the burden of glucocorticoid-associated side effects and associated cardiovascular risk factors, if the novel protocol is not inferior to the standard therapy regarding sustainment of remission. If our hypothesis turns out to be true, this novel therapy has the potential to become the standard of care for the initial treatment of SSNS in children.

Methods/design

Aim

The main purpose of the study is to show that MMF in the initial treatment of SSNS in children is not inferior regarding maintenance of initial remission and subsequent relapse rate compared to the standard prednisone regimen.

Study design

This is a prospective, randomized, multicenter, controlled, open, parallel group phase III non-inferiority trial.

After initiation of the study, patients will be screened consecutively and eligible patients will be enrolled into the study at each center.

Each sites' principal investigator has to declare to the coordinating investigator/sponsor that he/she will conduct the study according to the protocol, ethical rules, and to provide the support as needed. To minimize a potential performance bias, this will be fixed in a contract prior to commencing the study. The clinical monitor will introduce the sites in detail to study procedures and documentation in advance.

Bias by potential influential factors will be addressed by inclusion as covariates into the statistical analysis. Independent clinical on-site monitoring to ensure patients safety and integrity of the clinical data in adherence to study protocol will focus on source data documentation, correctness of data, and adherence to study procedures, e.g. randomization

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and treatment.

Based on the performed interventions and planned analysis blinding is not feasible to minimize bias, because the interventions can easily be differentiated due to visible side effects such as obesity, which is only expected in the standard care group. Furthermore, MMF is used in liquid form as a suspension and prednisone as a tablet. However, the primary endpoint is based on standardized diagnostic work-up results, i.e. objective criteria.

The duration of the study for each subject is expected to be 27 months (including 24 months follow-up after intervention). (Figure 1 and Figure 2)

Patient and public involvement

Patients were not directly involved in the study development and design. Repeated discussions with patient representatives beforehand showed one of their main wishes that is reduction of steroids in the treatment of nephrotic syndrome.

We generated an information document for parents in form of a flyer that was distributed also to patient initiatives. Spreading out information on the study shall improve recruitment. There is no patient adviser involved in the conduct of the study, neither was the burden of the intervention assessed by patients or their parents during study development.

Study results will be published open access. Patients and their representatives will be informed through meetings and a brief summary of the results distributed by local investigators.

Recruitment

The study is conducted on a multicenter basis. The rarity of the disease requires a nationwide recruitment. The planned 35 study centers are evenly distributed over Germany. Each study center is coordinating a number of collaborating hospitals and practitioners that will transfer eligible patients with primary onset steroid-sensitive nephrotic syndrome for

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screening, enrollment, randomization and study visits. 400 patients should be assessed for eligibility, 340 subjects should be enrolled in the clinical study, i.e. 170 subjects per treatment group.

Inclusion criteria and exclusion criteria

Inclusion criteria

Subjects meeting all of the following criteria will be considered for admission to the study:

- First episode of SSNS
- *Remission induced by prednisone or prednisolone 60 mg/m^2 BSA (maximum 80 mg/day) per day within 28 days*
- Male and female children aged ≥ 1 year and ≤ 10 years at beginning of the study (typical age range of patients with SSNS)
- Ability of the persons having care and custody of the child to understand character and individual consequences of clinical study
- Written informed consent of the persons having care and custody of the child (must be available before enrollment in the study)

Exclusion criteria

Subjects presenting with any of the following criteria will not be included in the study:

- Secondary nephrotic syndrome
- Estimated glomerular filtration rate (eGFR) <90 mL/min x 1.73 m^2 BSA
- Ongoing treatment with systematically administered glucocorticoids or other immunosuppressive drugs at time of first episode of nephrotic syndrome
- Hemoglobin concentration of ≤90 g/L (SI unit)
- Leucocyte count of ≤2.5 x 10^9/L (SI unit)
- Severe chronic gastrointestinal disease
- History of hypersensitivity to MMF or to any drug with similar

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chemical structure or to any excipient present in the pharmaceutical form of suspension of MMF (CellCept® suspension)

- Refusal of subject
- Participation in other clinical studies or observation period of competing studies

Study medication

The sponsor, i.e. the University Hospital Heidelberg, will provide the required study medication (mycophenolate mofetil, CellCept® suspension). Careful records will be kept of the study medication supplied to the centers and distributed to the patients.

Prednisone is used as standard therapy following the definition of the *GPN* (standard treatment) and is prescribed as usual.

- Prednisone or prednisolone (control intervention)

- MMF is administered in liquid form (CellCept® suspension (Roche Registration Ltd.)) (experimental intervention)

Adherence

Adherence will be recorded by the patients' diary.

Screening

All patients who seem suitable for study participation and take part in the screening will receive a screening number and will be registered in a screening log. Together with the center ID this will be the unique identification number throughout the study.

Parents of children with initial episode of idiopathic nephrotic syndrome aged between 1 and 10 years and treated with standard regime (prednisone 60 mg/m^2 BSA per day) will be informed about

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the ongoing INTENT study. If the child fulfills the inclusion criteria the persons having care and custody of the child and the patient, if ≥6 years of age, will be formally elucidated about the INTENT study by the study center in a form understandable to him or her and asked for written assent/consent.

For checking the exclusion criteria concerning eGFR, leucocyte count and hemoglobin concentration the most recent lab values should be used; they should have been obtained no more than 28 days prior to visit 1.

Randomization

To achieve comparable intervention groups, patients will be allocated in a concealed fashion by means of randomization using a centralized web-based tool (www.randomizer.at). Randomization will be performed stratified by age groups (grouped: <7 years of age, ≥7 years of age), because age is known to influence the occurrence of relapses. If the randomizer is not available in urgent cases the Institute of Medical Biometry and Informatics can be contacted and a biometrician or data manager will perform the randomization.

Intervention

Maximum duration of treatment is 12 weeks after first day of initial treatment of SSNS. (Figure 1)

Control intervention

• Prednisone, which is continued for a total of 6 weeks with the dosage of 60 mg/m^2 BSA/d (maximum 80 mg), is given twice per day or three times per day

plus

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- Prednisone, which is given for another total of 6 weeks with the dosage of 40 mg/m^2 BSA (maximum 60 mg) on alternate days (every other day) in one dose in the morning

Resorption of prednisone is independent of food intake.

Experimental intervention

- MMF is given in a dosage of 1200 mg/m^2 BSA/d as a suspension (200 mg/mL) until 12 weeks total treatment duration. MMF is given twice a day, i.e. every 12 hours (± one hour)
- The suspension of MMF is prepared in the study center (according to the summary of product information)
- The persons having care and custody of the child are informed that MMF should be given 30 minutes before or 60 minutes after food intake.
- For the first two weeks from randomization on, prednisone is given with the dosage of 40 mg/m^2 BSA (maximum 60 mg) on alternate days (every other day) in one dose in the morning.
- *At Visits 2 and 3 MPA-exposure is measured by a limited sampling strategy (blood samples are obtained at time points 0, 1 and 2 hours after intake of MMF*

Recording of primary endpoint

Daily dipstick testing of urine (Albustix®) and documentation in a standardized diary by a person having care and custody of the child is common current practice in the care of patients with nephrotic syndrome in pediatric nephrology centers.

No guideline exists on whether standard relapse treatment with prednisone should be started immediately when definition of relapse is fulfilled to avoid the associated complications of an

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edematous relapse or whether treatment should be delayed for several days to determine whether proteinuria resolves spontaneously. Therefore, in the INTENT study a time period of up to 10 days is allowed for a possible spontaneous remission, before standard therapy for relapse is started.

Treatment of a relapse has to be performed according to standard therapy of the *GPN* (prednisone 60mg/m² BSA [max 80mg] per day until the urine is free of protein for 3 consecutive days, followed by alternate day prednisone 40mg/m² BSA [max 60mg] for 4 weeks). Relapses with and without treatment are documented in the eCRF.

Treatment of frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome with other medications than prednisone is carried out according to center practice, because there is no internationally accepted guideline on this topic. The performed treatment with immunosuppressive agents such as CSA, tacrolimus, MMF, cyclophosphamide, rituximab, or levamisole is documented in the eCRF.

After completion of the study, patients will be treated according to center practice.

Outcome measures

Primary study endpoint

The primary efficacy endpoint is occurrence of a treated relapse within 24 months after completion of initial treatment. The rationale is that this endpoint was chosen in all previous studies on the initial treatment of SSNS in children and is also the primary endpoint in various meta-analyses on this topic.[3–5, 7, 8]

Definition of relapse: Relapse is denoted by a reappearance of proteinuria for 3 consecutive days:

Albustix® ≥2+ (first or second morning urine)

or

urine protein/creatinine (Up/c) ratio ≥2 g/g (first or second morning urine)

or

urine protein excretion of ≥40mg/m² BSA/h (urine collection for minimum 12 hours)

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Relapses with and without treatment are documented. The primary endpoint is fulfilled by the first treated relapse.

Secondary endpoints

Secondary endpoints are divided into five items:

1. Course of the disease as described by the following criteria
    a. Time from remission to first relapse
    b. Number of relapses during follow-up
    c. Mean relapse rate per patient and year
    d. Number of frequent relapsers
    e. Time from remission to intensification of immunosuppressive treatment with other drugs due to glucocorticoid-induced toxicity
    f. Rate of patients who require more intense immunosuppressive treatment (e.g. CSA, tacrolimus, MMF, cyclophosphamide, rituximab, or levamisole)
2. Glucocorticoid-associated toxicity:
    a. Cumulative prednisone dose as mg/m^2
    b. As there is no validated score for glucocorticoid-induced toxicity, each item is registered separately. At study visits 1-8, body mass index, blood pressure, and growth will be checked for quantitative influence, striae, hypertrichosis, acne, and psychological disturbances by yes or no for qualitative influence. Additionally, at study visits 1, 5, and 8, patients will be checked for cataract and glaucoma (by yes or no).
3. MMF-associated toxicity: At all visits, patients will be checked for known side effects of MMF, especially diarrhea, blood cell count disturbance, and infections.

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4. Health-related quality of life, which may be impaired in children with nephrotic syndrome will be measured with a validated questionnaire (DISABKIDS) at visits 1/5/8.
5. Days missing school attendance and days of hospitalization will be documented as a measure for the impact of the disease on everyday life.

It is expected that the MMF-based regimen will avoid acute and long-term glucocorticoid-associated toxicity and is therefore superior regarding the benefit/risk ratio. However, this will not be tested confirmatorily, since there is no endpoint or score summarizing the different aspects of side effects.

Statistical considerations

Sample size calculation

The sample size calculation is based on the primary efficacy endpoint "occurrence of a treated relapse within 24 months after completion of the initial treatment". In the literature varying information is given regarding the relapse rate for the control group receiving standard prednisone therapy. We have decided to assume a relapse rate of 51% according to Gipson et al.[8] The same rate is expected for the experimental group. If the relapse rate in the experimental group accounts to less than 15% above the relapse rate of the control group, this will be considered as clinically irrelevant based upon clinical judgement. Therefore the margin is set to δ=0.15. As the direction of the difference to be established is known for non-inferiority studies and as - due to the rareness of the disease and the related limited available number of patients - the study could otherwise not be performed with sufficient power, a one-sided significance level of 5% is applied. Testing at a one-sided significance level of α = 5% and aspiring a power of 80%, a total of 272 patients (136 per group) are required (calculations performed with ADDPLAN 6.0). To account for a 10% drop-out rate and major protocol violations in a further 10%, 340 patients will be randomized.

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Adherence/Rate of loss of follow up

The nephrotic syndrome in children is mostly an acutely presenting disease, and parents are very concerned about their child. With standard prednisone treatment we observe a high adherence to therapy. According to our previous experience in performing studies in pediatric nephrology we assume that a minimum of 85% of patients assessed for eligibility will be allocated to the study [4, 5, 22]. Due to the exclusive care of these patients in specialized pediatric nephrology centers we calculate with a loss of follow-up either due to drop-out or major protocol violation of maximum 20% which corresponds to our previous studies.[4, 5, 22] The recent study of the GPN, showing that MMF is efficacious in sustaining remission in children with frequently relapsing nephrotic syndrome, had only a drop-out rate of 4%. Therefore, for the entire study, we estimated 400 children with steroid-sensitive nephrotic syndrome to be assessed for eligibility, 340 to be allocated to study and 272 patients to be analyzed per protocol. However, in cases of premature withdrawal by a patient the persons having care and custody of this patient will be asked for informed consent so that routinely recorded data by the covering physician can be used for the INTENT study. In this manner as many data as possible is recorded for evaluation of treatments in this rare disease.

Analysis populations

The primary analysis will be performed for both the per-protocol population (PP) and the intention-to-treat population (ITT). The PP population comprises all patients, who were treated according to the randomized treatment as outlined in the protocol without major protocol violations (e.g., reduction of study medication of >50% or interruption of study medication of >3 days, violation of in- or exclusion criteria).The ITT population will comprise all patients randomized into the study. In this set, every patient is analyzed according to the group randomized into.

Since there may be patients who withdraw from the study after the treatment period or within the treatment period but consent to the analysis of routinely recorded data was given the inclusion of these patients into the ITT population will be decided case by case before database lock and defined

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when writing the statistical analysis plan (SAP). As appropriate, a third population will be defined for analysis of the primary and important secondary endpoints. How to deal with these patients and their data in detail depends on the time point of withdrawal and the amount and reliability of the routinely collected data.

The safety set will comprise all patients who have received study medication at least once, and will allocate the patients to the treatment they actually received, regardless of randomization. Whether routinely collected data of patients who withdraw prematurely can be included herein depends on the reliability of the collected safety data.

Statistical methods

The non-inferiority of the experimental group *vs.* control group will be evaluated using the test according to Farrington and Manning. The one-sided significance level is set to 5%.

The hypotheses to be assessed in the primary efficacy analysis are formulated as follows:

H_0: p_MMF – p_Prednisone ≥ δ (δ=0.15, non-inferiority margin, see sample size calculation for justification)

H_1: p_MMF – p_Prednisone < δ, where p_* denotes the relapse rate in the respective group.

Before database closure the assignment of patients to the PP population (patients with no major protocol violations) and the ITT population (as classified by the intent-to-treat principle) are defined in the statistical analysis plan. The confirmatory analysis is performed for both the PP population and the ITT population. This approach reflects the equal importance of both analysis sets in a non-inferiority trial. For the PP analysis missing values for the primary endpoint are not expected. In the ITT population missing values will be replaced according to Higgins.[23] As appropriate, a third population will be defined to adequately incorporate routinely collected data of patients who withdraw prematurely but gave informed consent for usage of routinely collected data. Details on

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inclusion of such data into sensitivity analyses of primary and secondary endpoints will be defined in more detail in the SAP. In case of uncertainty regarding data quality and reliability these patients will only be analyzed descriptively.

Additionally, binary logistic regression models will be performed as sensitivity analysis for the intervention comparison of the relapse rates adjusting for age, gender, center (grouped), and for results of therapeutic drug monitoring (grouped) based on different populations (PP, ITT, with values of drop-outs set to worst case).

All secondary outcomes will be evaluated descriptively, using appropriate statistical methods based on the underlying distribution of the data. Descriptive p-values are reported together with 95% confidence intervals for the corresponding effects. Descriptive statistics for continuous parameters and scores include number of non-missing observations, mean, standard deviation, median, minimum and maximum, performed for treatment groups as well as subgroups and overall. The description of categorical variables (ordinal or nominal) includes the number and percentage of patients belonging to the relevant categories in the study population as well as to each treatment group.

Rates of adverse and serious adverse events will be calculated with 95% confidence intervals for treatment group comparisons.

Statistical methods are used to assess the quality of the data, homogeneity of treatment groups, endpoints and safety of the two intervention groups. Details of the statistical analysis will be fixed at the latest in the SAP to be prepared within the first year after start of patient recruitment. All persons taking part in the preparation of the SAP and possible later changes to it will only have access to blinded data to avoid introduction of bias.

Interim Analyses

No interim analysis will be performed for the following reason: The recruitment phase is planned to be 36 months. The primary endpoint is occurrence of treated relapse within 24 months after end of

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initial treatment. Therefore, information on the primary endpoint for a first portion of the study patients will be available not before end of the recruitment phase. For this reason, a group-sequential approach was not pursued.

However, an independent data safety monitoring board (DSMB) will closely monitor the recruitment, the reported adverse events, the data quality of the study and the occurrence of potential early relapses during the intake of MMF, thus ensuring the ethical conduct of the study and protecting the safety interests of patients.

Adverse events

Adverse events (AEs) will be ascertained by the investigators using non-leading questions, noted as spontaneously reported by the patients to the medical staff or observed during any measurements on all study days. The observation period begins with the first administration of the Investigational Medicinal Product and ends with visit 4, (i.e. 6 months after day 1 [= first day of treatment with standard therapy]). The patient or his primary care physician should report any AE during the outpatient period via phone to the investigator.

AEs will be documented in the patient file and in the electronic case report form (eCRF). All subjects who present AEs,

whether considered associated with the use of the study medication or not, will be monitored by the responsible investigator to determine their outcome; this applies to withdrawals, too.

All serious adverse events (SAEs) and their relevance for the benefit/risk assessment of the study will be evaluated continuously during the study and for the final report.

All SAEs must be reported by the investigator to the Department of Pharmacovigilance at the Coordination Center for Clinical Trials (KKS) Heidelberg within 24 hours after the SAE becomes known using the "Serious Adverse Event" form.

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Suspected unexpected serious adverse events (SUSARs) are to be reported to the responsible ethics committee, the competent authority and to all participating investigators within defined timelines, i.e. they are subject to an expedited reporting.

All SAEs will be subject to a second assessment by a designated person or his deputy, who will be independent from the reporting investigator.

Data management

Data management and quality assurance

The investigator or a designated representative must enter all protocol-required information in the eCRF. The eCRF should be completed as soon as possible after the information is collected, preferably on the same day when a study subject is seen for an examination, treatment, or any other study procedure. The reason for missing data should be provided. The investigator is responsible for ensuring that all sections of the eCRF are completed correctly and that entries can be verified in accordance with the source data. Any entry and correction in the Remote Data Entry System will be documented automatically in an audit file.

Completeness, validity and plausibility of data will be checked in time of data entry (edit-checks) and using validating programs, which will generate queries. The investigator or the designated representatives are obliged to clarify or explain the queries. If no further corrections are to be made in the database it will be closed and used for statistical analysis. All data management procedures will be carried out on validated systems and according to the current Standard Operating Procedures (SOPs) of the Institute of Medical Biometry and Informatics (IMBI) of the University of Heidelberg.

Ethical and Legal Aspects

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that all persons involved in the study abide by

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International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use harmonized tripartite guideline on Good Clinical Practice (ICH-GCP) and the ethical principles described in the applicable version of the Declaration of Helsinki.

The study will be carried out in conformity with the ICH Topic E6, Guideline for Good Clinical Practice, including post Step 4 errata, September 1997, Directive 2001/20/EC (April 4, 2001), Commission Directive 2005/28/EC (April 8, 2005), National regulatory requirements/guidelines of the participating countries concerning Clinical Studies [e.g. federal drug law (AMG), GCP ordinance (GCP-Verordnung), Medical device law (MPG)], general national regulatory requirements, e.g. Bundesdatenschutzgesetz (BDSG).

Ethics committee approval

Ethical approval of the INTENT study was granted by the ethics committee of the Medical Faculty of the University of Heidelberg (AFmu-554/2014) on March 18, 2015. This approval has subsequently been confirmed by the local ethics committees of all participating centers.

The latest version of the trial protocol (version 5.0) was approved by the ethics committee on June 01, 2016.

Approval of the regulatory authorities

According to the German Federal law the study was approved by the Federal Institute of Drugs and Medical Devices on April 02, 2015 (reference number 61-3910-4040246). The latest version of the trial protocol (version 5.0) was approved by the Federal Institute of Drugs and Medical Devices on July 11, 2016.

Discussion

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Risk-benefit Assessment

Neither intensification nor prolonging initial therapy has influenced long-term prognosis of SSNS in terms of number of relapses and risk of frequent relapses [12–15]. MMF is effective in sustaining remission in patients with frequently relapsing steroid-sensitive nephrotic syndrome [16, 21, 22]. Therefore we hypothesize that after initial remission is achieved the risk for immediate relapse will not be increased in the experimental group. If a patient of the experimental group develops a relapse under MMF therapy he or she will be given prednisone anyway for induction of remission; the overall prognosis would therefore not be influenced. On the other hand, the patients in the experimental group may have the potential to benefit significantly because of less glucocorticoid-associated toxicity.

The most frequently observed side effects of MMF are gastrointestinal symptoms such as nausea, vomiting, stomach pain and diarrhea and hematological symptoms such as leukopenia, anemia and rarely thrombocytopenia and an enhanced susceptibility for infections. In general, these side effects occur more frequently and have a higher clinical significance, when MMF is administered in conjunction with other immunosuppressive medication such as CSA or tacrolimus, as indicated after solid organ transplantation. When MMF is administered as monotherapy, for example in patients with frequently relapsing steroid-sensitive nephrotic syndrome, the frequency and severity of these side effects are markedly lower [16–21]. Side effects will be systematically evaluated during the trial visits.

In order to acknowledge recently reported adverse events (hypogammaglobinemia, bronchiectasis, the risk of terato- and mutagenity) in patients after solid organ transplantation and treated with MMF in conjunction with other immunosuppressive medications in the long-time run, these adverse events are also monitored closely in the INTENT study, despite these events are very unlikely to occur due to the short administration period of MMF (max. 11 weeks) and the age group being tested in this trial.

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The oral formulation of MMF being a suspension allows exact and flexible dosing and reliable administration even to small children.

Cost-benefit analysis

The costs for a treatment with mycophenolic acid for an average time of 74 days (84 days of initial treatment minus an average of 10 days till remission) in a child with a body surface area of 0.8 m² in Germany are approximately ten times higher than the standard treatment with prednisone (500 € compared to 50 €). With the expected 250 new cases of childhood nephrotic syndrome per year this would mean extra costs of about 110.000 € for the German health care system. On the other hand, it has been shown that excessive weight gain during the initial steroid therapy in a significant subset (47%) of patients after cessation of glucocorticoid therapy persisted and thus contributes to long-term cardiovascular risk.[10, 11] These potential extra costs are hardly to be calculated but it seems reasonable enough to avoid long-term effects of high dose prednisone treatment.

Potential impact

The current study continues the long-lasting tradition of prospective randomized trials on the initial treatment of idiopathic nephrotic syndrome performed by the *GPN* (formerly *Arbeitsgemeinschaft für Pädiatrische Nephrologie*).

This is the first trial worldwide that prospectively evaluates a steroid-reduced initial treatment alternative that has the potential to reduce the number of side effects without lacking efficacy. If our hypotheses turn out to be true, the experimental therapy has the potential to become the future standard of care.

Optimizing recruitment

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Our structure of numerous study centers covering entire Germany that collaborate with regional hospitals and practitioners should make most new manifestations of idiopathic nephrotic syndrome available to study evaluation.

Nevertheless patient recruitment currently stays behind schedule. One aspect to improve recruitment is initiation of further study centers especially in densely populated areas in Southern Germany. Other aspects are strengthening the motivation of collaborating partners to transfer patients, advertising the study in widely distributed journals, by personal contact via mail and phone and to introduce the study at all suitable annual conferences. If patient recruitment cannot be increased sufficiently by these measures the recruitment period has to be prolonged.

Dissemination

The study results will be published in accordance with the CONSORT statement and SPIRIT guidelines. Our findings will be submitted to major international pediatric nephrology and general pediatric conferences and submitted for publication in a high impact factor journal with open access.

Trial status

The recruitment of the study started in October 2015.

As of June 12, 2018 a total of 156 children have been recruited into the study.

List of abbreviations

AAP	American Academy of Pediatrics
AE	Adverse event
AMG	Arzneimittelgesetz (German Medicinal Products Act)
APN	Arbeitsgemeinschaft für Pädiatrische Nephrologie

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BMBF	Bundesministerium für Bildung und Forschung (German Federal Ministry of Education and Research)
BSA	Body surface area
CSA	Cyclosporine A
DSMB	Data safety monitoring board
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ESPED	Erhebungseinheit für Seltene Pädiatrische Erkrankungen in Deutschland (German registry of rare pediatric diseases)
GCP	Good Clinical Practice
GPN	Gesellschaft für Pädiatrische Nephrologie (Society of Pediatric Nephrology)
ICH-GCP	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use harmonized tripartite guideline on Good Clinical Practice
IMBI	Institute of Medical Biometry and Informatics
IMPDH	Inosine monophosphate dehydrogenase
ITT	Intention-to-treat
KDIGO	Kidney Disease| Improving Global Outcomes
MMF	Mycophenolate mofetil
MPA	Mycophenolic acid
MPG	Medizinproduktegesetz (Act on Medical Devices)
PP	Per-protocol
SAE	Severe adverse event
SAP	Statistical analysis plan
SOP	Standard Operating Procedure
SSNS	Steroid-sensitive nephrotic syndrome

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SUSAR	Suspected unexpected severe adverse event

Declarations

Ethics approval and consent to participate

Ethics approval of the INTENT study was granted by the ethics committee of the Medical Faculty of the University of Heidelberg (AFmu-554/2014) on March 18, 2015. Informed consent will be/has been obtained from all participants.

Consent for publication

Not applicable.

Availability of data and material

http://www.intent-study.de

Competing interests

RE, MRB, JD, AF, JG, DH, BH, PFH, BK, MJK, MK, SL, UQ and AS declare to have no competing interests. BT and LTW have received research grants from Roche Pharma AG and Novartis AG.

Funding

The INTENT study is funded by the German Federal Ministry of Education and Research (BMBF, funding reference number 01KG1301).

Authors contributions

MRB, LTW, BT, JD, JG, DH, BH, PFH, MJK, MK, UQ, AF, AS, RE designed the study. AS, MRB, RE, BT and LTW will undertake data analyses. BK and SL gave advice in regulatory affairs and in realization of the

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study. RE, MRB, BT and LTW wrote the first draft of this manuscript, which has been critically revised by all co-authors. All authors have read and approved the final version of the manuscript.

Acknowledgements

Not applicable.

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Legends to figure 1 and 2:

Figure 1: Trial schema. On alternate days = every second day, BSA = body surface area

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Figure 2: Study visit schedule. TDM MPA = therapeutic drug monitoring of mycophenolic acid, ABPM = ambulatory blood pressure monitoring, HRQoL = health related quality of life, *only in the experimental group

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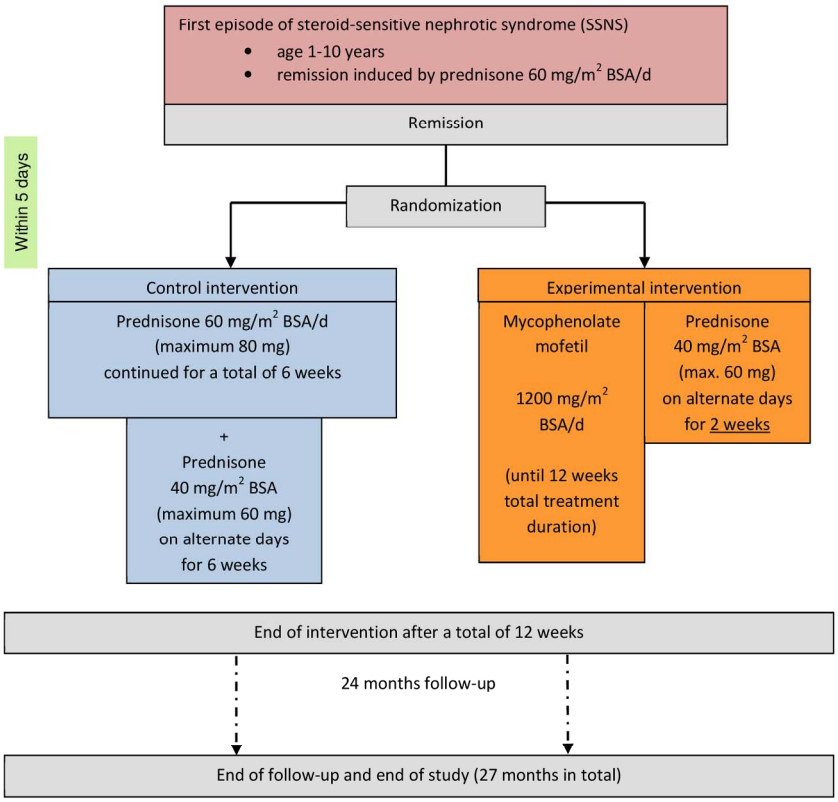

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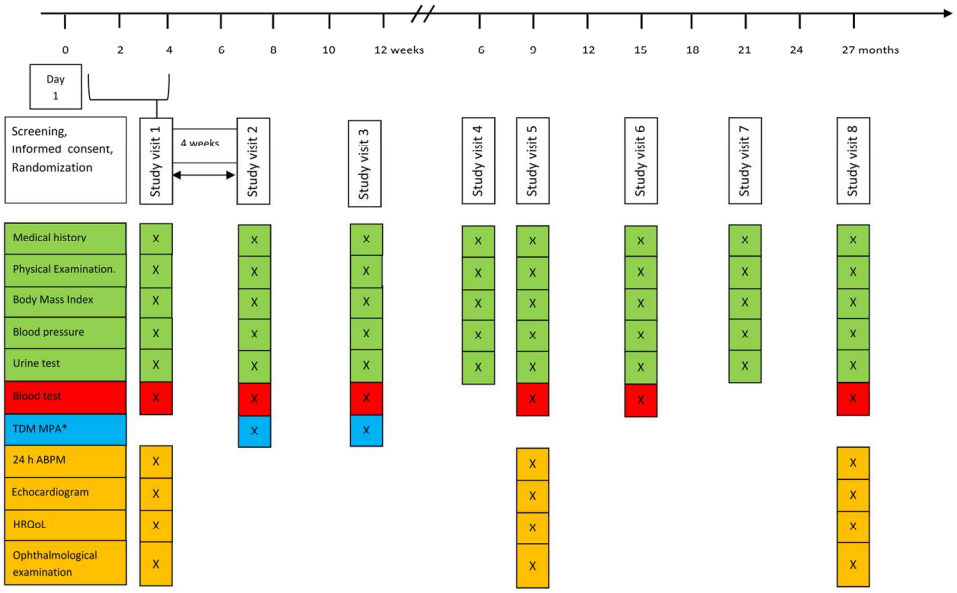

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____5_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____-_____
Protocol version	3	Date and version identifier	_____
Funding	4	Sources and types of financial, material, and other support	_____4_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____1-3_____
	5b	Name and contact information for the trial sponsor	see study protocol
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____

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Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_____6,7_____
	6b	Explanation for choice of comparators	_____9_____
Objectives	7	Specific objectives or hypotheses	_____8_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____9_____

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	___10_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_____10,11__
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____13_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_see study protocol___
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____12_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____14-16__
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	__Figure 2__

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____16_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10, 25
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____12_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____12____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____12_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	not applicable
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_see study protocol_____

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____21_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__17-19_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17-19
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	__see study protocol_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_20_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	20-21_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_see study protocol_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	__27_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_see study protocol_____

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____12_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___27_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____-_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	See study protocol___
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____-_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__-_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_27_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	yes_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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